REMARKS

The Examiner provides a number of allegedly new rejections:

I. Claims 1, 13, 15-22 and 25-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Benning (Ann. Rev. Plant Physiol. Plant Mol Biol, 49:53-75 (1998) and Essigmann *et al.* (Archives Biochem Biophys, 369: 30-41 (1990)) in view of McNally *et al.* (PNAS USA, 85:7270-7273 (1988)).

II. Claims 23-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Benning and Essigmann *et al.* in view of McNally *et al.*, as applied to claims 1, 13, 15-22 and 25-29 above, and further in view of Bidney *et al.* (United States Patent No.: 6,265,638, filed Sept. 28, 1999).

III. Claims 1, 13, 15-16, 26-31 and 40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Benning and Essigmann *et al.* in view of McNally *et al.*, as applied to claims 1, 13, 15-22 and 25-29 above, and further in view of Bevan *et al.* (Accession No.: AL137189, published July 27, 2000).

IV. Claims 32-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Benning, Essigmann *et al.*, McNally *et al.* and Bevan *et al.*, as applied to claims 1, 13, 15-16, 26-31 and 40 above, and further in view of Bidney *et al.*

This Office Action bears strong resemblance to prior 35 U.S.C. § 103(a) rejections the Examiner now admits are meritless. The prior office action response overcame the Examiner's obviousness rejections without claim amendments. But the Examiner has again burdened the Applicants with MORE REFERENCES (McNally *et al.*, Dong *et al.*, Yue *et al.* and Kovach *et al.*). Of these new references, the Examiner uses only one (*i.e.*, McNally *et al.*) as a tertiary reference in combination with Benning, Essigmann *et al.*, Bidney *et al.*, and Bevan *et al.*; all old references.

Arguments presented in previous office action responses have repeatedly overcome these old reference combinations (especially Benning and Essigmann *et al.*). The Applicants fail to understand how re-presenting these old references with immaterial new references either: i) modifies the analysis, or ii) rectifies deficiencies already established on the record. The

Applicants again emphasize the fact that the MPEP provides strong guidelines for an Examiner to provide the best references simultaneously and in the first office action.[1]

I. The Examiner Has Ignored Certain Claim Limitations

As a preliminary matter, when dealing with a rejection based upon obviousness it is essential for the Examiner to view the claimed embodiment as a whole:

> [T]he question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention *as a whole* would have been obvious.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871 (Fed. Cir. 1983) (emphasis in the original). It is clear to the Applicants that the Examiner has not "stepped back" from the elements to actually "see" the claimed embodiment. Specifically, the Examiner creates the obviousness rejections by "picking and choosing" specific elements among the cited publications and subsequently uses the specification in hindsight[2]. The Federal Circuit has noted that: "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Applicants note that the Examiner's conclusions allegedly establishing a *prima facie* case of obviousness are not supported by cited reference quotations (discussed more below).

It appears, moreover, that the Examiner has ignored certain claim limitations. While the Examiner continues to (incorrectly) allege that co-transformation is routine, the Examiner apparently fails to note that the claims involve enzymatic reactions where a product is produced. For example, Claim 17 requires more than merely generating a transformed host cell. Claim 17 requires that "sulfoquinovosyl diacylglycerol is produced by said transformed host cell." Thus, the Examiner's citation to references that merely teach transformation is insufficient. Furthermore, to the extent that the references cited by the Examiner a) reveal problems in generating a product, and/or b) admit the use of a special system that is not generally applicable, such references actually teach away.

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1 This is the sixth (6) Office Action in the context of two (2) Requests For Continuing Examination.

2 A practice not permitted under patent law. *See, In re Rouffet, 149 F.3d 1350, 47 USPQ.2d 1453 (Fed. Cir. 1998); and In re Warner,* 379 F.2d 1011, 154 USPQ 173 (CCPA 1967).

1. Benning & Essigmann *et al.* Fail As A Primary Combination

The Examiner's four obviousness rejections all depend upon the Benning and Essigmann *et al.* combination. The Applicants argue that both references fail to disclose the method claimed. Applicants again point out that the Examiner (in previous Office Actions) has admitted to the deficiencies of these references:

1. The Examiner admits that the primary reference, Benning, "does not teach a method of producing UDP-SQ from UDP-glucose with the polypeptide encoded by SEQ ID NO:6." (previous Office Action, p. 3).

2. The Examiner points to nothing in Benning about the expression of *both* genes in a host cell.

3. Essigmann is cited merely for the SQD1 gene; again, the Examiner points to nothing in about the expression of *both* genes in a host cell.

4. The Examiner admits that Essigmann teaches that the sulfur donor is unknown; the Examiner apparently (incorrectly) considers it sufficient under patent law that "sulfite is a *plausible* sulfur donor."

The Examiner, in the present Office Action, makes some statements which do not appear to be correct. For example, the Examiner states that "Benning teaches that sqdX from Synechoccoccus sp. catalyzes the reaction of UDP-SQ into SQDG. Sqdx is identical to SEQ ID NO:1 of the instant invention, *as evidenced by Guler et al. ." Office Action, pg. 2.*(emphasis added). It is not clear what "as evidenced by Guler" is meant to indicate. Guler *et al.* provides no sequence information regarding *sqd*X:

> These two results provide sufficient evidence to conclude that the sqdX gene product is essential for cyanobacterial sulfolipid biosynthesis, at least in *Synechococcus* and presumably also in *Synechocystis*.

Guler et al., pg. 454, 1st paragraph. Clearly, Guler *et al.* speaks solely from a functional viewpoint, not a structural one, and provides no teaching regarding the manufacture and use of recombinant proteins.

Neither can the Examiner make the argument that *sdq*X proteins are obvious from one species to another. Benning, in fact, provides additional evidence indicating that *sqd*X proteins in *Synechococcus* and *Synechocystis* are not identical in either nucleic acid sequence (*i.e.,* also amino acid sequence) or genomic location:

> However, we identified a novel sulfolipid gene in *Synechococcus sp.* PCC7942, designated *sqd*X, by inactivation of an open reading frame following directly the 3' end of *sqd*B ... Moreover, in *Synechocystis sp.* PCC6803, the putative *sqd*B gene **is not followed** by an open reading frame similar to *sqd*X. However, a putative coding sequence with **73% identity to *sqd*X** is located approximately 1.8Mb away from the putative *sqd*B gene in the genome of *Synechocystis sp.* PCC6803 ...

Benning, pg 59, paragraph 1 [emphasis added]. Essigmann *et al.* also fails to teach an *sqd*X recombinant protein.

Consequently, Benning, Essigmann *et al.*, and Guler *et al.*, fail to: i) disclose all the claimed elements, ii) provide a motivation to find the claimed elements; or iii) provide reasonable expectation of success. Moreover, the tertiary reference offered by the Examiner do not solve these deficiencies. The Applicants demonstrate below that the three additional references offered by the Examiner (*i.e.*, McNally *et al.*, Bishop *et al.* and Bevan *et al.*) do not disclose sufficient additional teachings to create a *prima facie* case of obviousness.

2. The Tertiary References Do Not Teach An Enzymatic Pathway

The Examiner cites McNally *et al.* primarily for the proposition that "...co-expression in *E. coli* **may prove** to be a useful approach for studying macromolecular assembly ..." *Office Action, pg. 3* [emphasis added]. First, the Applicants suggest the Examiner consider the conditional language used in the above quotation. The phrase, "may prove" is clearly a prediction, not a present day reality. The Examiner's reliance, therefore, on McNally *et al.* to establish that protein co-expression is well known in the art is mere wishful thinking. Second, McNally *et al.* limits the prediction to proteins undergoing macromolecular assembly.[3] McNally *et al.* is silent regarding the creation of a *enzymatic* pathway *so as to generate a product* - let alone the particular enzymes claimed and the particular product generated. Thus, and therefore adds nothing to the Benning/Essigmann *et al.* combination.

The Examiner (again) argues that Bidney *et al.* "... teach a method of co-expressing heterologous proteins ... using binary or multiple vectors ... [and] ... offers the potential to regenerate transgenic cells at relatively high frequencies ..." *Office Action, pg. 5.* Whether it "offers the potential" or not, there is not a SINGLE example among the seven (7) examples in Bidney *et al.* that involves co-expression of two enzymes in a pathway *to synthesize a product.* This point was previously made - and yet the Examiner points to nothing in rebuttal. Thus, Bidney *et al.* adds nothing to the Benning/Essigmann *et al.* combination.

The Bevan *et al.* reference merely discloses sulfolipid pathway protein amino acid and nucleic acid sequences. As a naked GenEmbl report, no teachings are present to make and use these sequences to create an enzymatic pathway.

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[3]McNally also had to resort to some tricks to even get the very limited system to work, using the heavy chain from slime mold together with the light chain from scallop.

3. Dong *et al.*, Kovach *et al.*, and Yue *et al.* Add Nothing

The Examiner does not cite Dong *et al.*, Kovach *et al.*, and Yue *et al.* in the context of a rejection but asserts them in an attempt to establish the level of skill in the art regarding protein co-expression. *Office Action, pg. 3.* The Applicants protest citing these references because none contain the Examiner's assertions. The Examiner either did not read these references or did not understand their contents.

Dong *et al.* does not conclude that protein co-expression is well known and practiced in the art. In fact, Dong *et al.*, concludes that their co-expression experiment was tantamount to failure:

> In contrast, many P450's, and in particular human P450 2E1, are poorly expressed in *E. coli.* The reason for this low content is not known ...

Dong *et al., pg. 258*, and

> The inability to demonstrate activity *in vivo* with whole cells is troubling. ... The generation of active, heterologous monoxygenase systems in live bacteria thus remains one of the challenges of contemporary biotechnology.

Dong *et al., pg. 259.* There is no question that Dong *et al.* believes many problems remain in the art in regards to successful protein co-expression.

Kovach *et al.* contains no conclusions that protein co-expression is well known and practiced in the art. In particular, Kovach *et al.* contains no teaching regarding co-expression of proteins to create an enzymatic pathway.

The Examiner overstates the Yue *et al.* reference in claiming this reference teaches that protein co-expression is well known and practiced in the art. Instead, Yue *et al.* merely offers a suggestion that co-expression might be tried:

> We propose that the approach used here **may perhaps be used** for coexpression of other mammalian protein modifying enzymes, such as protein methylases and acetylaces and their substrates.

Yue *et al.*, pg. *v* [emphasis added]. Further, Yue *et al.* explicitly teaches that protein co-expression is in fact, not routine:

> Although ASF/SF2 was phosphorlyated by SRPK1 in *E. coli*, we encountered problems in reproducibly obtaining bacteria transformed by the two expression vectors used in the above-presented results. We believe the reason for this is ... that expression of either one or both of the proteins is **toxic** to the bacteria.

Yue *et al.*, pg. *iii* [emphasis added]. The Applicants again conclude that the Examiner has not considered each reference in a thoughtful manner.

4. Conclusion

The Applicants show above that the Benning/Essigmann *et al.* primary combination contains fatal deficiencies that are not rectified by McNally *et al.*, Bidney *et al.* and Bevan *et al.* Further, the Examiner has failed to show that protein co-expression is routine and well known in the art by offering Dong *et al.*, Kovach *et al.* and Yue *et al.* The Examiner has failed to establish

a *prima facie* case of obviousness even with a combination of eight (8) references. The Applicants, therefore, respectfully request the Examiner pass all pending claims to allowance.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: July 26, 2004

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